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# Fatigue, depressive symptoms, and hopelessness as predictors of adverse clinical events following percutaneous coronary intervention with paclitaxel-eluting stents<sup>☆</sup>

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## Abstract

**Objective:** We investigated the relative effects of fatigue, depressive symptoms, and hopelessness on prognosis at 2-year follow-up in percutaneous coronary intervention (PCI) patients. **Methods:** Consecutively admitted PCI patients ( $n=534$ ) treated with paclitaxel-eluting stent as the default strategy completed the Maastricht Questionnaire (MQ) at baseline. Apart from an overall vital exhaustion score, the MQ also assesses fatigue (seven items; Cronbach's  $\alpha=.87$ ) and depressive symptoms (seven items; Cronbach's  $\alpha=.83$ ), with hopelessness (one item) comprised in the depressive symptom items. Patients were followed up for adverse clinical events (mortality and nonfatal myocardial infarction) at 2 years. **Results:** At 2-year follow-up, there were 31 clinical events. In univariable analyses, overall vital exhaustion and depressive symptoms, but not fatigue, were associated with adverse prognosis; in multivariable analysis,

depressive symptoms [hazard ratio (HR)=2.69; 95% confidence interval (95% CI)=1.31–5.55] remained the only predictor of clinical outcome. Among the depressive symptoms, hopelessness (HR=3.44; 95% CI=1.65–7.19) was the most cardiotoxic symptom. The incidence of clinical events was higher in the high-hopelessness patients (11% vs. 3%;  $P=.001$ ) than in the low-hopelessness patients. Hopelessness (HR=3.36; 95% CI=1.58–7.14;  $P=.002$ ) remained an independent predictor of clinical outcome at 2 years in adjusted analysis. **Conclusion:** Symptoms of depression, but not fatigue, predicted adverse clinical events. Hopelessness was the most cardiotoxic symptom, associated with a more than three-fold risk of clinical events 2 years post-PCI. Screening for hopelessness may lead to the identification of high-risk patients.

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**Keywords:** Coronary artery disease; Depressive symptoms; Fatigue; Hopelessness; Percutaneous coronary intervention; Prognosis

## Introduction

In the context of coronary artery disease (CAD), there is an ongoing debate as to whether depressive symptoms reflect actual depression or symptoms of underlying disease, given the overlap between depression and somatic symp-

toms, such as fatigue, trouble sleeping, and so on [1,2]. Fatigue [3–6], depression [1], and hopelessness [7,8] have all been associated with CAD. Fatigue is a frequently reported symptom in patients with cardiac conditions, with prevalence rates ranging from 59% to 75% [9]. Fatigue has been shown to precede the onset of myocardial infarction (MI) [3] and to be a risk factor for ischemic heart disease and mortality in healthy individuals [4]. In CAD patients, fatigue or exhaustion confers a two-fold to three-fold increased risk of morbidity and mortality, adjusting for clinical risk factors including disease severity [5,6].

<sup>☆</sup> No conflict of interest exists.

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Fatigue in patients with cardiac conditions has primarily been assessed with the Maastricht Questionnaire (MQ), which taps symptoms of exhaustion, demoralization, and increased irritability [10]. However, evidence suggests that the MQ assesses not only symptoms of fatigue but also symptoms of depression [11,12]. Given that depression is a risk factor for adverse clinical outcome in CAD [1,2,13], it is possible that depressive symptoms, as assessed by the MQ, may predict prognosis above and beyond fatigue. Previous attempts addressing this issue have primarily been performed at a conceptual level and have yielded inconsistent results [11,12,14–16].

Knowledge of the nature of depressive symptoms is important for secondary prevention in order to optimize risk stratification in clinical practice. Hence, there is a quest for the identification of the core and most cardiotoxic depressive symptoms. In epidemiological studies, hopelessness has been associated with the progression of carotid atherosclerosis [17,18], risk of mortality, and incidence of MI and cancer [7,19]. Although hopelessness may be considered a feature of depression, the strength of association with established depression scales is weak, suggesting that this psychological symptom should be studied in its own right [19]. To our knowledge, only one study has examined the role of hopelessness in the clinical course of CAD in patients with established disease and has found hopelessness to be associated with reduced survival [8]. However, this study did not compare the influence of fatigue relative to the influence of depressive symptoms and hopelessness.

Hence, in the current study, we investigated the relative effect of fatigue, depressive symptoms, and hopelessness on prognosis in patients treated with percutaneous coronary intervention (PCI).

## Materials and methods

### *Participants and study design*

Consecutively admitted patients presenting with stable or unstable angina, treated with PCI at the Erasmus Medical Center Rotterdam (Rotterdam, The Netherlands) between July 1, 2003, and July 1, 2004, qualified for inclusion in the current study. Implantation with paclitaxel-eluting stent comprised the default strategy. During this period, 845 patients were treated; patients who died within the first 4 weeks after the index procedure ( $n=19$ ) or who were not sufficiently proficient in the Dutch language to complete a psychological questionnaire ( $n=116$ ) were excluded. The remaining surviving patients ( $n=710$ ) were approached in writing and asked to complete the MQ 4 weeks post-PCI, which, in the remainder of the article, will be referred to as baseline; 536 (response rate, 75%) agreed to participate. Patients were followed up for clinical adverse events for 2 years.

Excluded patients and nonresponders on the MQ were more likely to smoke (22% vs. 14%;  $P=.003$ ) but were less likely to suffer from dyslipidemia (63% vs. 74%;  $P=.001$ ) than responders. No other differences were found between excluded/nonresponders and responders on baseline characteristics, including cardiac medication.

The hospital medical ethics committee approved the protocol. All patients provided written informed consent, and the study was carried out to conform with the Helsinki Declaration.

### *Demographic and clinical variables*

Demographic variables comprised sex and age. Information on clinical variables, [i.e., indication for PCI (stable or unstable angina), previous MI, previous coronary artery bypass graft (CABG) surgery, previous PCI, stent type (paclitaxel-eluting stent or other), multivessel disease, hypertension, dyslipidemia, diabetes mellitus, smoking, and cardiac medications such as aspirin, angiotensin-converting enzyme (ACE) inhibitors,  $\beta$ -blockers, diuretics, and statins] was obtained from medical records.

### *Fatigue, depressive symptoms, and hopelessness*

The 21-item MQ, administered at baseline, was used to evaluate overall vital exhaustion and symptoms of fatigue, depression, and hopelessness [10]. Items were answered on a 3-point scale (0=no, 1=?, 2=yes), with the total score ranging from 0 to 42. The reliability of the total scale is good (Cronbach's  $\alpha=.89$ ) [5]. Research suggests that the MQ predominantly assesses two symptom dimensions: fatigue and depression [11]. We could replicate these findings in the current study (Table 1). A principal components analysis (varimax rotation with scree plot criterion to determine the number of factors to extract) indicated two dominant dimensions, and both scales had good internal consistency, as measured by Cronbach's  $\alpha$ : (I) fatigue (seven items; Cronbach's  $\alpha=.87$ ; variance=36.4%) and (II) depressive symptoms (seven items; Cronbach's  $\alpha=.83$ ; variance=8.0%). Hopelessness was assessed with Item 10 of the MQ (i.e., "Have you experienced a feeling of hopelessness recently?"). Previous studies have also used one or two items to assess hopelessness as a risk factor for the onset of CAD [7,8,17,18].

### *Clinical end point*

The end point was defined as a clinical adverse event (all-cause mortality or nonfatal MI) 2 years post-PCI.

### *Statistical analysis*

Comparisons of baseline characteristics stratified by hopelessness (using the highest tertile to indicate a high score) were performed using chi-square test (Fisher's exact test, when appropriate) for nominal variables and Student's  $t$  test for independent samples for continuous variables.

Table 1  
Symptoms of fatigue and depression, as assessed by the MQ

Item	Factor analysis	Reliability <sup>a</sup>	MQ item number
<b>Fatigue (Factor I)</b>			
1. Do you often feel tired?	.76	0.69	1
2. Do you have a feeling that you have not been accomplishing much lately?	.75	0.69	5
3. Do you feel weak all over?	.71	0.69	4
4. I feel fine (reverse).	.71	0.68	14
5. Do you feel more listless lately than before?	.68	0.67	8
6. Do you have a feeling these days that you just do not have what it takes any more?	.65	0.58	17
7. Do you sometimes feel that your body is like a battery that is losing its power?	.63	0.58	15
		Cronbach's $\alpha=.87$	
<b>Depressive symptoms (Factor II)</b>			
1. Would you want to be dead at times?	.76	0.57	16
2. Do you feel you want to give up trying?	.72	0.59	13
3. Do you feel dejected?	.68	0.66	18
4. Do you believe that you have come to a "dead end"?	.66	0.66	7
5. Do you feel like crying sometimes?	.60	0.50	19
6. Have you experienced a feeling of hopelessness recently?	.56	0.57	10
7. Do you ever wake up with feelings of exhaustion and fatigue?	.49	0.46	20
		Cronbach's $\alpha=.83$	

Factor loadings are presented in italics.

<sup>a</sup> Corrected item–total correlations (Cronbach's  $\alpha$ =estimate of internal consistency).

Univariable and multivariable Cox regression analyses were used to examine the predictive value of the total MQ scale (21 items) and the MQ subscales fatigue (seven items) and depressive symptoms (seven items), using both continuous and dichotomized scores. When using dichotomized scores, we used the standardized cutoff of  $\geq 14$  for the total MQ [20] and the highest tertile to indicate clinically manifest symptoms on the separate fatigue and depressive symptom dimensions, respectively. In all multivariable analyses, we adjusted for sex, age, multivessel disease, previous cardiac history, hypertension, dyslipidemia, diabetes, and smoking. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported.  $P<.05$  was used to indicate statistical significance. All tests were two-tailed. All analyses were performed using SPSS 12.0.1.

## Results

Of the 536 patients, two patients did not have a score on the hopelessness item of the MQ and were therefore excluded from further analyses.

## Baseline characteristics

Baseline characteristics stratified by hopelessness are shown in Table 2. Patients who scored high on hopelessness were younger, were more likely to have had a previous cardiac history, and were more likely to have been prescribed ACE inhibitors. No other differences on demographic and clinical characteristics were found between high-hopelessness patients and low-hopelessness patients.

## Fatigue, depressive symptoms, and clinical events

At 2-year follow-up, there were 31 (21 deaths and 10 nonfatal MIs) clinical events.

In univariable analyses using dichotomized scores, depressive symptoms, but not fatigue, were significantly associated with the incidence of death and nonfatal MI at 2-year follow-up (Fig. 1). Subjecting these subscales and the original MQ scale (assessing vital exhaustion, cutoff of  $\geq 14$ ) to a multivariable Cox regression analysis using a stepwise procedure, depressive symptoms (HR=2.69; 95% CI=1.31–5.55;  $P=.007$ ), but not fatigue and vital exhaustion, were associated with clinical outcome (Table 3). A stepwise procedure was chosen in order to extract the component(s) that exerted the most toxic influence on prognosis.

Table 2  
Baseline characteristics stratified by hopelessness

	High hopelessness ( <i>n</i> =187)	Low hopelessness ( <i>n</i> =347)	<i>P</i>
<b>Demographic characteristics</b>			
Male (%)	68	74	.20
Age in years [mean (S.D.)]	61 (11)	64 (11)	.002**
Married/partner (%)	81	81	1.00
<b>Clinical variables (%)</b>			
Paclitaxel-eluting stent <sup>a</sup>	90	88	.53
Multivessel disease	60	60	1.00
Cardiac history <sup>b</sup>	62	52	.04*
Hypertension	45	50	.35
Dyslipidemia	73	74	.87
Diabetes mellitus	24	18	.12
Smoking	18	12	.06
<b>Cardiac medication (%)</b>			
Aspirin	93	96	.15
ACE inhibitors	16	6	<.001***
$\beta$ -Blockers	25	21	.26
Diuretics	2	1	.81
Statins	77	73	.39

<sup>a</sup> Paclitaxel-eluting stent was used as the default stent (i.e., in 89% of the total sample). The other stents used were sirolimus-eluting stent (4%), both paclitaxel-eluting stent and sirolimus-eluting stent (1%), or bare-metal stent/balloon dilation (6%).

<sup>b</sup> MI, PCI, or CABG prior to the index event.

\*  $P<.05$ .

\*\*  $P<.01$ .

\*\*\*  $P<.001$ .

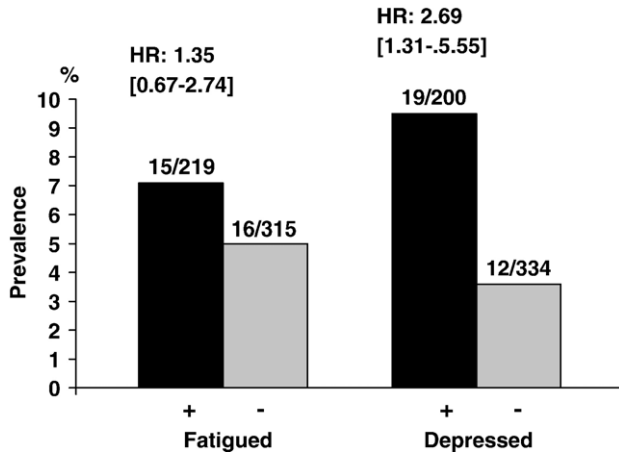


Fig. 1. Death/MI stratified by fatigue and depressive symptoms. \*Numbers are presented on top of bars.

### Hopelessness and clinical events

Given the possibility that the predictive value of depressive symptomatology might be attributed to specific symptoms such as hopelessness, we performed a series of univariable analyses using continuous scores of the items. Only the symptoms “hopelessness” and “wanting to be dead” were significant predictors of death/MI (Table 4). In a multivariable analysis with a stepwise procedure subjecting all depressive symptom items as continuous scores, the only symptom that was retained was “hopelessness” (MQ 10; HR=1.93; 95% CI=1.33–2.80;  $P=.001$ ). Since “hopelessness” and “wanting to be dead” (i.e., the only two items that were significant predictors in univariable analyses) could potentially be equally important cardiotoxic depressive symptoms, we entered both in a multivariable analysis, together with baseline characteristics. However, only hopelessness (HR=1.91; 95% CI=1.28–2.86;  $P=.02$ ), but not “wanting to be dead” (HR=0.97; 95% CI=0.62–1.48;  $P=.88$ ), was associated with adverse clinical events

Table 3  
Baseline symptoms and death/MI (31 events) at 2 years post-PCI

	HR [95% CI]	P
(A) Univariable analysis		
Subscale scores		
Fatigue	1.35 [0.67–2.74]	.40
Depressive symptoms	2.69 [1.31–5.55]	.007**
Total MQ score		
Vital exhaustion	2.73 [1.17–6.33]	.02*
(B) Multivariable analysis <sup>a</sup>		
Significant		
Depressive symptoms	2.69 [1.31–5.55]	.007**
Nonsignificant		
Fatigue		.42
Vital exhaustion		.29

<sup>a</sup> Stepwise procedure.

\*  $P<.05$ .

\*\*  $P<.01$ .

Table 4

Predictive value of specific depressive items in relation to death/MI at 2 years post-PCI<sup>a</sup>

	HR [95% CI]	P
1. Hopelessness (MQ 10)	1.89 [1.31–2.74]	.001**
2. Wanting to be dead (MQ 16)	1.59 [1.07–2.37]	.02*
3. Feeling dejected (MQ 18)	1.24 [0.83–1.85]	.30
4. Feeling like crying (MQ 19)	1.19 [0.81–1.75]	.38
5. Waking up exhausted (MQ 20)	1.16 [0.80–1.69]	.43
6. Wanting to give up trying (MQ 13)	1.15 [0.77–1.71]	.50
7. Coming to a “dead end” (MQ 7)	1.07 [0.71–1.62]	.75

<sup>a</sup> Univariable analyses, using continuous scores for depressive items.

\*  $P<.05$ .

\*\*  $P<.01$ .

on follow-up. After dichotomizing the hopelessness symptom, with the highest tertile representing clinically manifest symptomatology, the incidence of clinical events was 11% (20 of 187) in high-hopelessness patients versus 3% (11 of 347) in low-hopelessness patients ( $P=.001$ ). Hopelessness was associated with a more than three-fold risk (HR=3.44; 95% CI=1.65–7.19;  $P=.001$ ) of adverse clinical outcome in univariable analysis (Fig. 2).

Entering the hopelessness symptom together with the rest of the subscale comprising the six other depression symptoms showed that hopelessness was an independent predictor of clinical events (HR=4.07; 95% CI=1.76–9.43;  $P=.001$ ), whereas the six-item depression score was no longer associated with death/MI (HR=0.73; 95% CI=0.32–1.63;  $P=.44$ ). In multivariable analysis, hopelessness (HR=3.36; 95% CI=1.58–7.14;  $P=.002$ ) remained an independent predictor of death/MI and was associated with a more than three-fold increased risk, adjusting for sex, age, multivessel disease, previous cardiac history, hypertension, dyslipidemia, diabetes, and smoking.

In the final analysis, we investigated whether the addition of hopelessness to a multivariable model, comprising demographic and clinical baseline characteristics, improved the level of prediction of death and MI on follow-up. As indicated by the  $-2$  log likelihood function, the level of

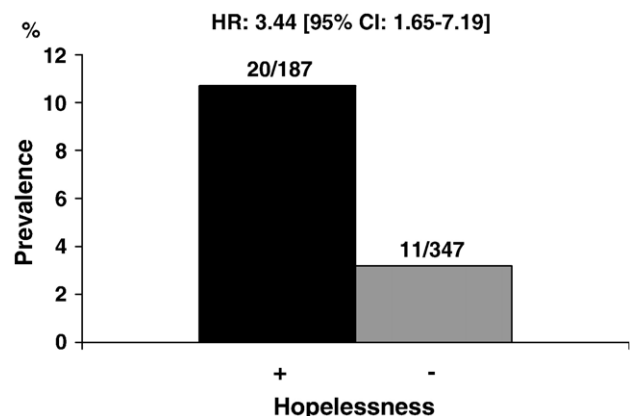


Fig. 2. Death/MI stratified by hopelessness. \*Numbers are presented on top of bars.



prediction of the model improved with the addition of hopelessness [ $\chi^2=10.420$  ( $df=1$ ),  $P=.001$ ].

## Discussion

To our knowledge, this is one of the first studies to have examined the relative effects of fatigue, depressive symptoms, and hopelessness on clinical events in patients with established CAD. In PCI patients treated with paclitaxel-eluting stents, we found that depressive symptoms, but not fatigue, were associated with adverse clinical outcomes, with the most cardiotoxic depressive symptom being hopelessness. Hopelessness was associated with a three-fold increased risk of death/nonfatal MI at 2 years in adjusted analyses.

The last decade has witnessed a surge in research on depression as a risk factor for CAD, leading to a call for the recognition of depression as an established risk factor [13]. Despite extensive research, we still know little about the nature of depressive symptoms and those that are most toxic in terms of predicting clinical outcomes. Hence, identification of the core and most toxic symptoms of depression is now receiving increased attention [1,2,21]. However, studies to date have been rather heterogeneous in their focus, ranging from deriving subscales from the Beck Depression Inventory (BDI) and relating them to clinical outcome [1], to comparing the predictive validity of instruments (BDI vs. the depression subscale of the Hospital Anxiety and Depression Scale) [2], to assessing whether depressive cognitions comprise an underpinning of depression in post-MI patients [21].

In the current study, we identified hopelessness as the depressive symptom that was most salient in predicting prognosis. PCI patients who scored high on hopelessness, as measured by one item on the MQ, had a more than three-fold increased risk of mortality and nonfatal MI 2 years postprocedure, independent of baseline demographic and clinical characteristics. Previous epidemiological studies also found that hopelessness was associated with the progression of carotid atherosclerosis [17,18], morbidity, and mortality [7,19], but to our knowledge, only one study has examined the impact of hopelessness as a risk factor in patients with established CAD [8]. In the latter study, hopelessness was also associated with decreased survival and was shown to exert an independent effect on prognosis relative to depressive symptoms. However, the study did not compare the influence of fatigue relative to depressive symptoms and hopelessness.

Physiological pathways through which hopelessness may exert its deleterious effect on health include decreased heart rate variability (particularly reduced vagal tone or parasympathetic activity) [22], impaired fibrinolysis [23], and inflammation [17]. In the latter study, plasma fibrinogen, a marker of systemic inflammation, was shown to mediate the relationship between hopelessness and

progression of carotid atherosclerosis. Compliance may comprise a behavioral pathway, given that depression has been shown to have a negative influence on adherence to cardiac rehabilitation [24] and medication [25]. However, whether these results extend to hopelessness needs to be confirmed in future studies.

Given the relatively high prevalence of fatigue and its deleterious effects on health [3–5,9], it is surprising that fatigue has not received more attention in the cardiovascular literature. Although we were not able to confirm that fatigue was associated with adverse prognosis in the current study, it is too premature to write off fatigue as a risk factor in CAD. The reason for the nonsignificant result may be due to the relatively small number of events in the current study, as the incidence of death and nonfatal MI was larger in fatigued patients than in nonfatigued patients. As voiced by others, there is an urgent need to develop measures of fatigue that tap these symptoms in patients with cardiac conditions without the confounding of related symptomatology [11]. With the availability of such measures, it will be possible to establish the salience of fatigue as a predictor of clinical events in CAD.

The findings of the current study have implications for research and clinical practice. Given that there is an inverse relationship between the length of a questionnaire and the response rate [26], when collating a test battery, it may be important to prioritize the inclusion of a measure of hopelessness if there is no room for a more lengthy measure of depressive symptoms. A two-item measure of depressive symptoms [i.e., the Patient Health Questionnaire (PHQ-2)], which includes hopelessness, has previously been shown to have good sensitivity and specificity, compared with the gold standard of a clinical diagnosis of depression, and to be sensitive to change [27]. The recent four-item Symptoms of mixed Anxiety–Depression Index (SAD<sub>4</sub>) also includes hopelessness [28] and has been shown to predict a clinical diagnosis of depression even when adjusting for depressive symptomatology, as measured by the BDI. However, neither the PHQ-2 nor the SAD<sub>4</sub> has yet been used as a potential predictor of clinical outcome in CAD. In terms of clinical practice, screening for hopelessness is feasible and can be incorporated into the daily routine of practicing cardiologists. PCI patients suffering from hopelessness need to be identified early on and to be followed more closely throughout in order to motivate them to participate in cardiac rehabilitation, as they may be more inclined to refuse participation or to drop out from rehabilitation programs [24]. In terms of intervention, it may be possible to reduce feelings of hopelessness using a cognitive–behavioral approach either on its own or in combination with pharmacotherapy, as hopelessness is predominantly considered a cognitive symptom of depression [29,30].

The current study has some limitations. First, for 42% of the patients, we had no information on left ventricular ejection fraction; therefore, in multivariable analyses, we were not able to adjust for measures of disease severity

but only for a measure of the extent of disease, as assessed by multivessel disease. Second, results may not be generalizable to MI patients, since only patients with stable or unstable angina as an indication for PCI were included. Nevertheless, the results of this study show that the assessment of psychosocial risk factors is also important in more low-risk patients, such as patients with angina, given their impact on adverse clinical events. Third, 25% of patients declined to participate. However, nonresponders and excluded patients (excluded due to lack of language proficiency) did not differ from responders on demographic and clinical baseline characteristics, except for nonresponders/excluded patients being more likely to smoke and less likely to suffer from dyslipidemia. Fourth, our multivariable model was overfitted given the number of adverse clinical events. Fifth, hopelessness was assessed by one item, but other studies have also used a one-item measure of hopelessness and have shown that hopelessness is a predictor of adverse clinical outcome [8]. Finally, although it may seem contrary to expectations that the item “Do you ever wake up with a feeling of exhaustion and fatigue?” loaded on the depression factor rather than on the fatigue factor, insomnia and fatigue both form part of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria for a major depressive disorder.

In conclusion, we found that depressive symptoms, but not fatigue, were associated with adverse clinical outcome in PCI patients treated with paclitaxel-eluting stents. More specifically, hopelessness proved to be the most cardiotoxic component and was associated with a more than three-fold increased risk of death and nonfatal MI at 2 years, after adjusting for demographic and clinical baseline characteristics. It is feasible to include the assessment of hopelessness in research protocols and clinical practice. Future studies that replicate these findings are warranted, given that few studies have examined the impact of hopelessness on patients with established CAD.

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